ISSN: 2581 – 3633
PubMed - National Library of Medicine - ID: 101745081

International Journal of Medical Science and Advanced Clinical Research (IJMACR)

Available Online at: www.ijmacr.com

Volume – 3, Issue – 5, September - October - 2020, Page No. : 163 - 170

Vain is Still a Clinical Dilemma: A Review Article

[1]Dr Vinita Singh, MS, Department of Obstetrics & Gynaecology Department, AIIMS Raipur

[2]Anu Singh, MD Pathology, RML, New Delhi

[3]Pragati Trigunait, Senior Resident ,Obstetrics & Gynaecology Department, AIIMS, Raipur

[4]Sagarika Majumdar, Senior Resident ,Obstetrics & Gynaecology Department, AIIMS, Raipur

[5]Dr Shikha Singh, Senior Resident, Obstetrics & Gynaecology Department, AIIMS, Raipur

Corresponding Author: Dr Vinita Singh, MS, Department of Obstetrics & Gynaecology Department, AIIMS, Raipur

Type of Publication: Original Research Article

Conflicts of Interest: Nil

Abstract

Vaginal intraepithelial neoplasia (VAIN) accounts for 0.4% of the lower genital tract intraepithelial disease. As a result of these low rates, management recommendations for IN of the vagina, vulva, and anus are based on relatively small prospective studies and retrospective series. Since vaginal carcinoma and VAIN are uncommon and abnormal vaginal cytology is rarely of clinical importance for the general population, new cervical cancer screening guidelines indicate that women who have undergone hysterectomy and have no history of CIN2+ should not be screened for vaginal cancer. However, limited data suggest that women who have had a hysterectomy for cervical cancer or CINs may be at an increased risk of local recurrent cancer or VAIN in up to 5% to 10% of cases. Although the five-year survival rates for stage I cervical cancer exceeds 90%, local recurrence rates are high, ranging from 10% to 20%. Due to all these clinical dilemmas and controversies, this article has focussed on the important points related to VAIN to manage our patients with a broader vision.

Keywords: Vaginal Intraepithelial Neoplasia (VAIN), Papanicolau test (PAP Test), Human Papillomavirus (HPV), Squamous Cell Carcinoma (SCC).

Introduction

One in every five women in the world suffering from cervical cancer belongs to India which has the largest burden of cervical cancer patients in the world.[1] India also has the highest age-standardized incidence of cervical cancer in South Asia .[2]The current data estimates indicate approximately 132,000 new cases diagnosed and 74,000 deaths annually in India, accounting for nearly 1/3rd of the global cervical cancer deaths.[3] The incidence of intraepithelial neoplasia (IN) of the lower genital tract has risen during the last four decades.[4] Vaginal intraepithelial neoplasia (VaIN) is a rare human Papillomavirus (HPV)-related premalignant condition, histologically diagnosed, characterized by dysplastic changes in the vaginal epithelium, without stromal invasion.[5]Vaginal carcinoma is an uncommon gynecologic malignancy, with an annual incidence of 0.69 per 100,000 female population[6.]and vaginal intraepithelial neoplasias (VAINs) are also rare, with an incidence of 0.2 to 0.3 per 100,000 women.[7- 11] Its natural history is not well known.[12]Vaginal intraepithelial neoplasia (VaIN) is a rare human Papillomavirus (HPV)-related premalignant condition, histologically diagnosed, characterized by dysplastic changes in the vaginal epithelium, without stromal invasion.[13] Although the risk factors for VaIN are similar

to those described for cervical intraepithelial neoplasia (CIN), its incidence appears to be 100-fold lower,[14] this is believed to be due to the lack of a vulnerable squamocolumnar junction in the vagina.[15] Additionally, it is speculated that HPV infection of the vagina occurs as frequently as in the cervix, but a lytic cell reaction in the vaginal epithelium enables the regression of lesions, in contrast to the characteristic latent infection in the cervix which causes persistent dysplasia.[16 -17] Invasive vaginal carcinoma is rare, accounting for only 1%– 4% of all gynecological malignancies .[18]For example, abnormal vaginal epithelial cytology was found in only 1.1% to 1.3% of vaginal cuff cytology testing in women hysterectomizrd for benign disease.[19-20] Therefore, abnormal vaginal cytology is rarely of clinical importance for the general population, and new cervical cancer screening guidelines recommend that hysterectomized women at any age who have no history of cervical intraepithelial neoplasia grade 2+ (CIN2+) should not be screened for vaginal cancer using any modality. Evidence of adequate negative prior screening is not required. [21] Most of the authors classified VaIN into low-grade lesions (mild dysplasia, VaIN 1) and high-grade lesions (high-grade vaginal intraepithelial neoplasia [HG-VaIN]: VAIN 2 and VaIN3, corresponding to moderate and severe dysplasia) according to the depth of tissue involved.[22-28] Test for screening VAIN are Cytologic testing used ThinPrep Pap tests (TPPTs), hrHPV DNA Screening Testing. In a study of 411 patients for disease progression and recurrence in women treated for vulvovaginal intraepithelial neoplasia (29.9%) recurred later than one year after initial treatment and 24 patients (5.8%) progressed to invasive disease. According to multivariate analyses, the risk factors associated with recurrence and progress to invasive disease were multifocality, immunosuppression, excision as initial treatment vs. laser evaporation, and smoking .[29]

Another study indicated that women with cervical cancer are at an increased risk of VAIN besides recurrence, and women with cervical SCC are more prone to high-grade VAIN/recurrence, especially within the first two years after hysterectomy. The significantly increased detection rate of VAINs/recurrence in the hrHPV-positive group suggests vaginal cytology and HPV co-testing might be the preferred method for surveillance in these women. [30] HPrevalence of HPV in VAIN 2/3 and VAIN1 is 92.6%, and 98.5%, respectively, higher than in vulvar lesions.HPV16 is the most common HPV type in vaginal (55.4%) cancers and VAIN2/3 (65.8%) 31 associated neoplasia of the lower genital tract (67.6 %) and history of prior hysterectomy (54.4%) can be present.[32] A recent comparative survey of cancer survival rates in Africa, Asia, and Central America based on patients diagnosed in the 1990s indicates substantially lower survival rates in parts of Africa, India, and the Philippines than for those diagnosed in Singapore, South Korea, and parts of China. [33]

Discussion

As a result of these low rates, management recommendations for IN of the vagina, vulva, and anus are based on relatively small prospective studies and retrospective series .[34-36] Since vaginal carcinoma and VAIN are uncommon[37-38] and abnormal vaginal cytology is rarely of clinical importance for the general population[39-40] new cervical cancer screening guidelines indicate that women who have undergone hysterectomy and have no history of CIN2+ should not be screened for vaginal cancer.[41] However, limited data suggest that women who have had a hysterectomy for cervical cancer or CINs may be at an increased risk of local recurrent cancer or VAIN in up to 5% to 10% of cases.[42-47]

Although the five-year survival rate for stage I cervical cancer exceeds 90%, local recurrence rates are high, ranging from 10% to 20%.[48-49]

Since patients with the locally recurrent disease can be offered salvage treatments with the potential for cure, the SGO and the ACOG recommend a review of symptoms and physical examination every three to six months for the first two years and a yearly Pap smear to detect local recurrence and preinvasive disease.[50-52] Along with clinical symptoms, a physical examination will detect most cases of local recurrent cancer. Retrospective studies have shown cytologic evaluation to be low yield for detecting recurrent cancer, with detection rates ranging from 0% to 17%.[53] Similar to CIN or cervical carcinoma, VAINs are also caused by HPV, especially hrHPV, since HPV types 16 and 18 accounts for most cases.[54-56] The prevalence of HPV in vaginal intraepithelial lesions parallels that of cervical intraepithelial lesions. [57-59] Cervical SCC is a risk factor for consequent high-grade vaginal epithelial lesions (VAIN2+), but cervical adenocarcinoma might not be a risk factor for high-grade vaginal epithelial lesions (VAIN2+). Although almost all cervical epithelial carcinoma (SCC, adenocarcinoma, and adenosquamous cell carcinoma) are caused by hrHPV infection, our data suggest that there might be a different pathogenic mechanism or genetic vulnerability between SCC and adenocarcinoma, and vaginal intraepithelial lesions might follow the same pathogenic mechanism as cervical SCC instead of just HPV infection.[60] our data indicate that women who had invasive cervical cancer are at an increased risk of high-grade VAIN lesions, especially those with cervical SCC. The tone of the first studies to investigate hrHPV testing during follow-up for women with invasive cervical carcinoma after hysterectomy, and the significantly increased detection rate of VAINs in the hrHPV-positive group suggests that vaginal cytology and HPV co-testing might be an effective detection method for these patients.[61] LDR brachytherapy is an effective and safe treatment for vaginal intraepithelial neoplasia.[62] The 3 main modalities reported were surgery, brachytherapy, and medical management. Surgery included local excision, laser ablation, vaginectomy, and cavitational ultrasonic ablation. Medical management included topical 5%imiquimod, 5-fluorouracil, and trichloroacetic acid. All treatments had success rates for disease clearance with low rates of progression to cancer. Prerequisites for ablative treatments are the lesions and adequately examined by a biopsy to exclude invasion. Where invasion is suspected and cannot be excluded (eg: at vault suture line), surgical excision is essential. Brachytherapy and vaginectomy, although effective have limited place because of their related morbidity. Treatment choice will depend upon the availability of equipment and expertise. [63] A cohort study done on 420 patients concluded that patients older than 50 years and with high-grade CIN should undergo biopsy from the upper 1/3 of the vagina at multiple points .[64]

CONCLUSION: VAIN is a rarely diagnosed condition mainly due to failure of regular follow-up and pap smear examination in post hysterectomy cases. . Therefore, Regular PAP smear is important in the diagnosis of stages of dysplasia in vaginal epithelium which if diagnosed at an earlier stage, carcinoma can be prevented. Still, large Prospective trials and Randomized control trials are required to reach to some conclusion.

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How to citation this article: Dr Vinita Singh, Anu Singh, Pragati Trigunait, Sagarika Majumdar, Dr Shikha Singh, "Vain is Still a Clinical Dilemma: A Review Article", IJMACR- September - October - 2020, Vol – 3, Issue -5, P. No. 163 –170.